Isosterism and bioisosterism in drug design

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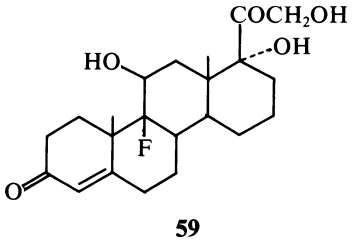
J. A. Salmon et al., *Progress in Drug Research / Fortschritte der Arzneimittelforschung / Progrès des recherches pharmaceutiques* © Birkhäuser Verlag Basel 1991

lar methyl groups and substitution by acetylenic groups at C-17 can change one hormonal activity into another (estrogen to progestational etc.). Most of these compounds are not isomers; should at least some of these structurally overall similar agents many of which act at related receptors be called bioisosteres? Such a claim would have to be supported by studies of the lipophilicity and other physical properties of paired series of steroid hormones.

1.6.1 Isosteric halogens

Fluorine differs from the other halogens by its smaller size which leans more towards the volume of hydrogen, and by its stable shorter bond to carbon. These properties have been taken advantage of in 9α- (or 12α)-fluorocortisols *(59)* which are several times as active in many respects as the parent hormones [121], but other modifications such as the introduction of methoxyl lead to the same results; yet fluorine and methoxy are not isosteric in the classical sense. The firm bond between fluorine and carbon also favors stability in trifluoromethyl compounds. Thus trifluoperazine *(60)* is a more potent neuroleptic than prochlorperazine *(61)* but the more pronounced electronegative



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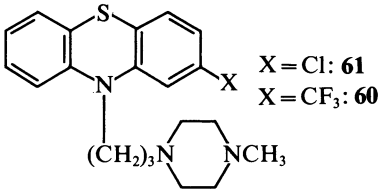
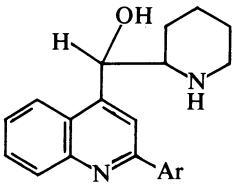


X = Cl: **61**
X = CF_3: **60**

character of trifluoromethyl probably accounts principally for this difference. Other highly electronegative groups (NO_2, SO_2CH_3) share this tendency, while electron-donating groups such as methyl are dystherapeutic. In many cases CF_3 substitution yields compounds that are less toxic than compounds with other electronegative substituents, and this has influenced the choice of test drugs to be prepared.
The trifluoromethyl group has played a role in molecular modification of quinine analogs. The antimalarial alkaloid, quinine, is deactivated by metabolic oxidation at position 2 of the quinoline ring.



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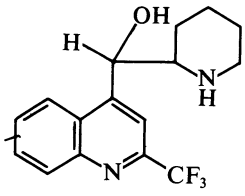

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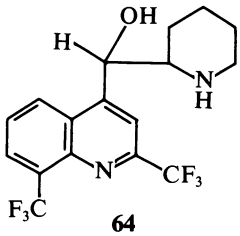

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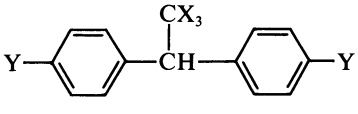
Blockade of this position by a variety of aromatic groups *(62)* regularly caused phototoxicity in the resulting derivatives and their analogues with a stripped-down piperidine ring [122]. It appeared possible that aryl substitution should be avoided and replaced by substitution with some other electron-rich but less conjugated structurally unrelated group. Trifluoromethyl was chosen as a test case *(63)* [123]. Although phototoxicity encountered in *62* was not eliminated completely, further substitution with CF_3 was undertaken because 3,6-bis(trifluoromethyl) substituted phenanthrene amino alcohols had shown a considerable increase in antimalarial activity over monotrifluoromethyl derivatives [124]. Empirical substitution in all benzenoid positions of the quinoline ring yielded the 2,8-bis (trifluoromethyl)quinoline piperidyl alcohol *64* (mefloquine) which has become an important antimalarial drug [125].

The relationship of fluorine, hydrogen, and other halogens is illustrated in a series of analogues of the contact insecticide, chlorophenothane (DDT) *(65)* in which the five chlorine atoms were systematically



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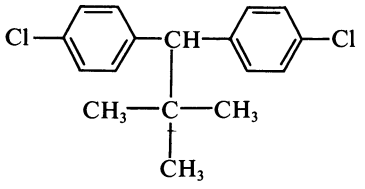
X = Y = Cl

exchanged for fluorine, bromine, and methyl. Here activity usually depends on the size of X, neurotoxic contact insecticidal activity being registered when X = Cl, Br or CH_3 with Y = Cl. No activity is found if X = F or H, but if Y = F and X = Cl, activity is comparable to Y = Cl or Br. However, if Y = F and X = CH_3, activity is lost [126], even though chlorine and methyl occupy comparable volumes [127]. This prediction is, however, confirmed in the bis(*p*-chlorophenyl)-*t*-bu-



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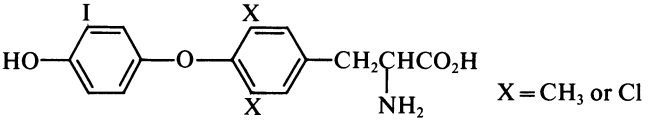
tylmethane analogue *66* which is as neurotoxic as chlorophenothane *(65)*. Possibly, steric factors are also involved, the trichloromethyl group of *65* and the *t*-butyl group of *66* bending the two aromatic nuclei out of the tetrahedral angle one expects for diphenylmethane.
In the non-phenolic ring of thyronine analogues, 3,5-dichloro substitution of *L*-T_3 in lieu of iodine produces an appreciable thyromimetic effect, and so does the 3,5-dimethyl derivative *(67)*. These substituents



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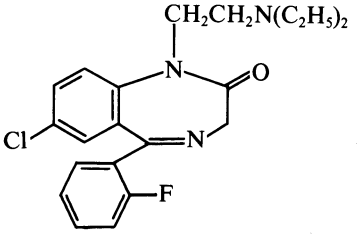
contribute to the hydrophobicity of the ring [128]. Binding free energy values of the dimethyl analogue of *L*-T_3 and the dichloro analogue of *L*-T_4 are almost identical [129]. It must be kept in mind, however, that methyl groups can be oxidized metabolically, especially if they are attached to an aromatic ring. This may affect the half-life in tests *in vivo*.
The overall effects of fluorine substitution are hard to predict. Flurethyl, bis(trifluoromethyl)ether, is a central stimulant with an action similar to the initial phase of diethyl ether. In the replacement of the *o*-chlorine atom in chlorazepam by fluorine, flurazepam *(68)* deepens sedative-hypnotic activity [130]. On the other hand, while chloroform ($CHCl_3$) is a general anesthetic, dichlorodifluoromethane (CCl_2F_2)



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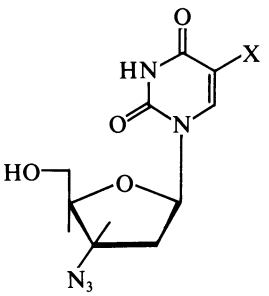
has little, if any, depressing or toxic properties. Here the lipophilic distribution may be the principal influence on activity.

3′-Azido-3′-deoxythymidine (AZT, zyvudine) *(69)* is a potent inhibitor of the replication of the human immunodeficiency virus (HIV) [131]. It is phosphorylated to the triphosphate which then inhibits the utilization of dTTP by reverse transcriptase and thereby prevents the elongation of viral DNA. Various 3′-azido nucleosides have been prepared and tested against HIV-1 in cell cultures; a few are listed in Chart 1. Of these modifications, AZT remained the most active drug. Trifluoromethyl substitution *(69 A)* that could be thought of as leading to a bioisostere, abolishes activity, whereas the halogen deriva-

Chart 1 [132]



X =	X =
H	$OCH_2CH=CH_2$ **(70)**
CH_3 **(69)**	$OCH_2C=CH$
CF_3 **(69 A)**	OCH_2CN
	SCH_3
F, Br, I **(69 B)**	SCN
OH	NH_2, $NHCH_3$
OCH_3	$N(CH_3)_2$
OC_2H_5	

tives (F, Br, I) *(69 B)* and the amino and hydroxyl compounds (other classical isosteres) retain significant antiviral potency. The allyl ether *70* analogue was highly active.

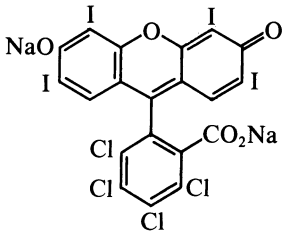
No clear relationship between antiviral activity and the electron-donating or electron-withdrawing capacities of the 5-substituents emerged from this study.

The replacement of chlorine by bromine in some drug structures generally, but not inevitably, deepens some biological actions, including toxicity. Bromide ion had been used as a calming sedative in the 19th century, and perhaps as a memory of this application some aliphatic bromo compounds such as diethylbromoacetylurea, $(C_2H_5)_2CBrCONHCONH_2$, and bromoisovalerylurea, $(CH_3)_2CHCHBrCONHCONH_2$, are still prescribed sporadically in some countries for this purpose. Chloral hydrate, $Cl_3CCH(OH)_2$, and chloroform are general anesthetics but the corresponding bromo compounds cannot be used. Here again, lipophilicity is the most import-

ant – at least the most widely studied – determinant in SAR. Force of inhibition of CNS enzymes may well shed more light on these questions. Thus, isosterism can be claimed for all the halogens but bioisosterism which postulates the similarity of biological properties cannot be predicted easily.

Two types of agents appear to depend on the presence of iodine in their molecules for useful activity. In the case of thyroid hormones, the several iodinated thyronines have not been rivalled by the corresponding bromo and chloro analogues. Enzymatic uptake of iodide and subsequent oxidative biosynthesis of the hormones is a process that has evolved over millions of years in aquatic and later in terrestrial animals. There is no reason to assume that other halogens could not participate in these natural reactions, but apparently this does not happen. That iodine is not unique in producing hormonal properties has been shown by synthesizing *D,L*-3,3′-diiodo-5-bromothyronine which increased the oxygen consumption of thyroidectomized rats and reduced the size of the thyroid gland in antigoiter tests [133]. *DL*-3,3′,5-Triiodo-5′-fluorothyronine, an H...F isostere of triiodothyronine (T_3), shows about one-third the effect of thyroxine by the goiter prevention method [134].

The other case is that of organic iodinated radiopaque agents. Iodine, in organic linkage, endows compounds with a greater capacity for x-ray opaqueness than do the other halogens. Nevertheless, tetrabromophenolphthalein was used briefly in cholecystography until the more effective isomeric tetraiodo compounds could be prepared. Phenoltetrachlorophthalein has also been used in hepatography [135], and so has Rose Bengal, the disodium salt of tetraiodotetrachlorofluorescein *(71)*.



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1.7. Limits of bioisosterism

By the early 1960's, some uncertainties had surfaced in the explanation and applications of bioisosterism. One apparent shortcoming was that what seemed to be a solid rule in one series of structurally related compounds failed to work out in a series with different overall structural characteristics. In such cases one could not predict whether one would end up with an agonist, a mixed agonist – antagonist, or an antagonist. Ariens [136] and Korolkovas [137] tried to list those structural moieties which often turn an agonist into an antagonist. However, they did not include the possibility that the bioisosteric planning process, i.e. experiments to rationally design a drug structure, may have disturbed one of several parameters that had proved to be necessary for inducing a given biological activity. Such parameters include size and bond angles (shape), ability to form hydrogen bonds at active sites of enzymes or drug receptors, pK_a, chemical reactivity, hydrophilicity, lipophilicity (i.e. maintenance of the same or at least similar partition coefficients), and also the metabolic fate of the compounds to be prepared. There are limits concerning the number of these parameters that can be changed unpunished. Yet the hope for potential success in bioisosteric exchanges has intrigued many medicinal chemists, even if they or their physical chemistry colleagues have not measured all the constants and values involved. This has led to a silent understanding that at least in early research in a given structural series one might postpone adhering to the more rigid requirements of classical isosterism.

The reasons for this apparent self-deception are practical realities of daily work. No two manufacturers of automobiles, computers, breakfast cereals, swimwear and other necessities of the good life will copy every feature of their competitors. Instead, they will try to improve some aspects of the original product and delete, or at least play down, any point that had elicited justified criticism. In order to achieve these guidelines, the properties of the product to be modified would have to be analyzed and understood as far as the state of the art permits.

It is the same with medicinal agents. One will rarely seek to obtain a drug with completely identical properties but almost always try to improve potency and specificity and decrease side effects and toxicity. Bioisosterism provides descriptions of electronic, steric, lipophilic,

and distribution characteristics of a compound, and these data help us to understand mechanisms of action and the role of a compound in producing measurable biological consequences. If the purpose of a research project is to come up with a drug that exhibits modifications of one or several properties and does not wholly match the model "lead" compound, then the description and definition of this "lead" compound will not suffice. At this point, human inventiveness and intuition and our gambling spirit as to which facet of the necessary properties we should change, will have to be brought into play. Experience in a structural field will be helpful in prompting our decision making. If we want to create a bioisosteric drug with some desirable changes, we will have to be aware of the fact that sooner or later we may step outside the limits of permissible classical bioisosteric alterations. As we transgress these limits we stand to lose activity altogether or sometimes, conjure up a totally new set of biological properties, some wanted, some undesirable, and usually baffling. The rules which delineate bioisosterism will point to compromise structures which may be just still acceptable as candidates. Such chemical structures are spoken of as non-classical bioisosteres. Their study and use has expanded steadily over the last several decades.
It will come as no surprise that reviewers of the subject of bioisosterism have given preference to either more biochemical or more physical aspects of the phenomenon [138, 139].

1.7.1 Interactions at receptor sites

One guideline how far we may venture in designing new drugs at the border of bioisosterism is provided by advances in our understanding of biochemical mechanisms at receptor sites. Receptors are glyco- and lipoproteins or, in some cases, nucleic acids. The protein receptors may be enzymes or membrane-spanning macropolypeptides. Active sites of enzymes are situated in the protein chains of these biocatalysts and are part of molecular bays formed by these chains. A drug or substrate has to fit more or less snuggly onto such harboring polypeptide bays and will try to make contact with the amino acid side chains or the amide groups of the peptide backbone. The side chains are SH groups, alcoholic and phenolic OH groups, amino and guanidino groups, carboxyls and carboxamide groups, and disulfide bridges which are partly responsible for the stereostructure of the enzyme.